Patent Application
Attorney Docket No. PC22013AADO

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: **Alasdiar M. Naylor, et al** :

APPLICATION NO.: **To be assigned** : Examiner: **To be assigned**

FILING DATE: **Filed herewith** : Group Art Unit: **To be assigned**

TITLE: **Treatment of Male Sexual Dysfunction** :

Hon. Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

IN THE SPECIFICATION

Please insert the following sentences after the Title and prior to the first line.

--This application is a continuation-in-part of U.S. application serial no. 09/895,367 which was filed on June 29, 2001 which claims priority from U.S. provisional application 60/265,358 which was filed on January 31, 2001 and United Kingdom application 0030647.2 which was filed on December 15, 2000. This application is also a continuation-in-part of U.S. application serial no. 09/905,846 filed July 13, 2001. This application also claims priority from U.S. provisional application 60/291,722 filed May 17, 2001, U.K. provisional application 0108730.3 filed April 6, 2001, U.K. provisional application serial no. 0109910.0 filed April 23, 2001, U.K. provisional application 0111037.8 filed May 4, 2001 and U.K. application 0120679.6 filed August 24, 2001.--

IN THE CLAIMS

Please Cancel Claims 1 and 2.

Please amend claim 3 as follows:

Claim 3 (Amended) A method according to claim 13 wherein said inhibitor when in use is highly selective for NPY/NPY Y1 located in male genitalia.

Please amend claim 4 as follows:

Claim 4 (Amended) A method according to claim 14 wherein said inhibitor has no, or substantially no, activity towards endopeptidase NEP and/or angiotensin converting enzyme.

Please amend claim 5 as follows:

Express Mail No. EL710829238US

Claim 5 (Amended) A method according to claim 14 wherein said treatment or prevention of MED is selective.

Please amend claim 6 as follows:

Claim 6 (Amended) A method according to claim 14 wherein an increase in intracavernosal pressure is observed.

Please amend claim 7 as follows:

Claim 7 (Amended) A method according to claim 14 wherein the medicament is administered by mouth.

Please amend claim 8 as follows:

Claim 8 (Amended) A method according to claim 13 wherein said inhibitor is when in use highly selective for NPY and/or NPY Y1 receptors associated with the corpus cavernosum.

Please amend claim 9 as follows:

Claim 9 (Amended) A method according to claim 14 wherein said NPY and/or NPY Y1 inhibitor is administered before and/or during sexual arousal.

Please Cancel claim 10.

Please amend claim 11 as follows:

Claim 11 (Amended) A pharmaceutical composition for use in the treatment of male erectile dysfunction comprising an inhibitor of a neuropeptide Y (NPY), which inhibitor when in use is selective for an NPY associated with male genitalia; wherein the inhibitor is admixed with a pharmaceutically acceptable carrier, diluent or excipient.

Please Cancel claim 12.

Please amend claim 14 as follows:

Claim 14 (Amended) A method according to claim 13 wherein the inhibitor is an NPY Y1 inhibitor.

Please amend claim 19 as follows:

Claim 19 (Amended) An assay according to claim 18 wherein said test agent selectively inhibits NPY or NPY Y1 receptors associated with the genitalia.

Please amend claim 20 as follows:

Claim 20 (Amended) A process comprising the steps of:

(a) performing an assay according to claim 18;

(b) identifying one or more agents capable of inhibiting NPY Y1; and

(c) preparing a quantity of those one or more identified agents; and wherein said agent is an NPY Y1i.

Please amend claim 24 as follows:

Claim 24 (Amended) A method of treating MED with an agent; wherein the agent is capable of inhibiting NPY Y1 in an *in vitro* assay method; wherein the *in vitro* assay method is the assay method defined in claim 23.

Please amend claim 25 as follows:

Claim 25 (Amended) An agent identified by the assay methods according to claim 23.

Please cancel claims 26-27.

Please amend claim 30 as follows:

Claim 30 (Amended) An animal model for identifying an agent capable of treating MED, said model comprising an anaesthetised animal including means to measure changes in intracavernosal pressure and/or cavernosal blood flow of said animal following stimulation of the pelvic nerve thereof; and wherein said agent is an NPYi or an NPY Y1i.

Please amend claim 32 as follows:

Claim 32 (Amended) An assay method for identifying an agent that can directly enhance the endogenous erectile process in order to treat MED, the assay method comprising: administering an agent to the animal model of claim 30; and measuring the change in the endogenous erectile process; wherein said change is defined as a potentiation of intracavernosal pressure (and/or cavernosal blood flow) in the animal model in the presence of a test agent as defined; and wherein said agent is an NPY Y1i.

Please amend claim 33 as follows:

Claim 33 (Amended) A method according to claim 13 wherein in addition to the treatment of MED, abnormal drink and food intake disorders, in particular obesity, anorexia, bulimia and metabolic disorders are also treated.

Please amend claim 34 as follows:

Claim 34 (Amended) A method for treating or preventing MED by administering a combination consisting of one or more NPYi's and one of the following auxiliary active agents to an individual:

(i) Naturally occurring or synthetic prostaglandins or esters thereof.;
(ii) α - adrenergic receptor antagonist compounds;
(iii) NO-donor (NO-agonist) compounds;
(iv) Potassium channel openers or modulators;
(v) Dopaminergic agents;
(vi) Vasodilator agents;
(vii) Thromboxane A2 agonists;
(viii) CNS active agents;
(ix) Ergot alkoloids;

(x) Compounds which modulate the action of natruretic factors;

(xi) Angiotensin receptor antagonists;

(xii) Substrates for NO-synthase;

(xiii) Calcium channel blockers;

(xiv) Antagonists of endothelin receptors and inhibitors or endothelin-converting enzyme;

(xv) Cholesterol lowering agents;

(xvi) Antiplatelet and antithrombotic agents;

(xvii) Insulin sensitising agents;

(xviii) L-DOPA or carbidopa;

(xix) Acetylcholinesterase inhibitors;

(xx) Steroidal or non-steroidal anti-inflammatory agents;

(xxi) Estrogen agonists and/or estrogen antagonists;

(xxii) A PDE inhibitor;

(xxiii) An NEP inhibitor;

(xxiv) Vasoactive intestinal protein (VIP), VIP mimetic, VIP analogue, one or more of a α-adrenoceptor antagonist with VIP combination;

(xxv) A melanocortin receptor agonist or modulator or melanocortin enhancer;

(xxvi) A serotonin receptor modulator;

(xxvii) A testosterone replacement agent, testosternone, dihydrotestosterone or a testosterone implant;

(xxviii) Estrogen, estrogen and medroxyprogesterone or medroxyprogesterone acetate (MPA), or estrogen and methyl testosterone hormone replacement therapy agent;

(xxix) A modulator of transporters for noradrenaline, dopamine and/or serotonin;

(xxx) A purinergic receptor agonist and/or modulator;

(xxxi) A neurokinin (NK) receptor antagonist;

(xxxii) An opioid receptor modulator;

(xxxiii) An agonist or modulator for oxytocin/vasopressin receptors;

(xxxiv) Modulators of cannabinoid receptors;

(xxxv) A bombesin receptor antagonist;

(xxxvi) A SEP inhibitor; or

(xxxvii) An agent capable of modulating the activity of an intermediate conductance calcium-activated potassium (IK_{Ca}) channel in the sexual genitalia of an individual.

Please amend claim 35 as follows:

Claim 35 (Amended) A method of treating or preventing MED by administering a combination consisting of one or more NPYi's and one or more PDEi's to an individual.

Please amend claim 36 as follows:

Claim 36 (Amended) A method according to claim 35 wherein said NPYi is an NPY Y1i.

Please amend claim 37 as follows:

Claim 37 (Amended) A method according to claim 36 wherein said PDEi is a PDE5i.

Please amend claim 38 as follows:

Claim 38 (Amended) A method according to claim 37 wherein the medicament is administered by mouth.

Please amend claim 41 as follows:

Claim 41 (Amended) A pharmaceutical composition according to claim 40 wherein said NPY Y1i is highly selective for NPY Y1 receptors associated with genitalia.

Please amend claim 42 as follows:

Claim 42 (Amended) A pharmaceutical composition according to claim 41 wherein said PDEi is a PDE5i.

Please amend claim 43 as follows:

Claim 43 (Amended) A pharmaceutical composition according to claim 42 wherein the composition is administered by mouth.

Please amend claim 44 as follows:

Claim 44 (Amended) A method of treating or preventing MED by administering a pharmaceutical composition according to claim 43.

REMARKS

Applicants respectfully request entry of the amendments herein above, and an early examination and allowance of the claims.

Attached hereto is a "Version with Markings to Show Changes Made."

Please charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this sheet are enclosed.

Respectfully submitted,

Date: 12/12/2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

PRELIMINARY AMENDMENT

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IN THE CLAIMS

Please Cancel Claims 1 and 2.

Please amend claim 3 as follows:

Claim 3 (Amended) ~~The use according to claim 1 or claim 2,~~ A method according to claim 13 wherein said inhibitor when in use is highly selective for NPY/NPY Y1 located in male genitalia.

Please amend claim 4 as follows:

Claim 4 (Amended) ~~The use according to any one of claims 1-3,~~ A method according to claim 14 wherein said inhibitor has no, or substantially no, activity towards endopeptidase NEP and/or angiotensin converting enzyme.

Please amend claim 5 as follows:

Claim 5 (Amended) ~~The use according to any one of the preceding claims~~ A method according to claim 14 wherein said treatment or prevention of MED is selective.

Please amend claim 6 as follows:

Claim 6 (Amended) ~~The use according to any one of the preceding claims~~ A method according to claim 14 wherein an increase in intracavernosal pressure is observed.

Please amend claim 7 as follows:

Claim 7 (Amended) ~~The use according to any one of the preceding claims~~ A method according to claim 14 wherein the medicament is administered by mouth.

Please amend claim 8 as follows:

Claim 8 (Amended) ~~The use according to any one of the preceding claims~~ A method according to claim 13 wherein said inhibitor is when in use highly selective for NPY and/or NPY Y1 receptors associated with the corpus cavernosum.

Please amend claim 9 as follows:

Claim 9 (Amended) ~~The use according to any one of the preceding claims,~~ A method according to claim 14 wherein said NPY and/or NPY Y1 inhibitor is administered before and/or during sexual arousal.

Please Cancel claim 10.

Please amend claim 11 as follows:

Claim 11 (Amended) A pharmaceutical composition for use in the treatment of male erectile dysfunction ~~(MED); the pharmaceutical composition~~ comprising an inhibitor of a neuropeptide Y (NPY), which inhibitor when in use is selective for an NPY associated with male genitalia; wherein the inhibitor is ~~optionally~~ admixed with a pharmaceutically acceptable carrier, diluent or excipient.

Please Cancel claim 12.

Please amend claim 14 as follows:

Claim 14 (Amended) A method according to claim 13 wherein the inhibitor is an NPY Y1 inhibitor.

Please amend claim 19 as follows:

Claim 19 (Amended) An assay according to ~~claim 17 or~~ claim 18 wherein said test agent selectively inhibits NPY or NPY Y1 receptors associated with the genitalia.

Please amend claim 20 as follows:

Claim 20 (Amended) A process comprising the steps of:

(d) performing an assay according to ~~any one of claims 17-19~~ claim 18;

(e) identifying one or more agents capable of inhibiting ~~NPY or~~ NPY Y1; and

(f) preparing a quantity of those one or more identified agents; and wherein said agent is ~~a NPYi or~~ an NPY Y1i.

Please amend claim 24 as follows:

Claim 24 (Amended) A method of treating MED with an agent; wherein the agent is capable of inhibiting ~~NPY or~~ NPY Y1 in an *in vitro* assay method; wherein the *in vitro* assay method is the assay method defined in claim 23 ~~any one of claims 22-23~~.

Please amend claim 25 as follows:

Claim 25 (Amended) An agent identified by the assay methods according to claim 23 ~~claims 17-19 or claims 22-23~~.

Please cancel claims 26-27.

Please amend claim 30 as follows:

Claim 30 (Amended) An animal model for identifying an agent capable of treating MED, said model comprising an anaesthetised animal including means to measure changes in intracavernosal pressure and/or cavernosal blood flow of said animal following stimulation of the pelvic nerve thereof; and wherein said agent is an NPYi or an NPY Y1i.

Please amend claim 32 as follows:

Claim 32 (Amended) An assay method for identifying an agent that can directly enhance the endogenous erectile process in order to treat MED, the assay method comprising: administering an agent to the animal model of claim 30 ~~or clam 31~~; and measuring the change in the endogenous erectile process; wherein said change is defined as a potentiation of intracavernosal pressure (and/or cavernosal blood flow) in the animal model in the presence of a test agent as defined; and wherein said agent is ~~an NPYi or~~ an NPY Y1i.

Please amend claim 33 as follows:

Claim 33 (Amended) A method according to claim 13 ~~The use according to any one of claims 1-10,~~ wherein in addition to the treatment of MED, abnormal drink and food intake disorders, in particular obesity, anorexia, bulimia and metabolic disorders are also treated.

Please amend claim 34 as follows:

Claim 34 (Amended) A method for treating or preventing MED by administering a ~~The use of~~ a combination consisting of one or more NPYi's and one of the following auxiliary active agents to an individual ~~in the manufacture/preparation of a medicament for the treatment or prevention of MED~~:

(i) Naturally occurring or synthetic prostaglandins or esters thereof.;

(ii) α - adrenergic receptor antagonist compounds;

(iii) NO-donor (NO-agonist) compounds;

(iv) Potassium channel openers or modulators;

(v) Dopaminergic agents~~, preferably apomorphine or a selective D2, D3 or D2/D_3agonist~~;

(vi) Vasodilator agents;

(vii) Thromboxane A2 agonists;

(viii) CNS active agents;

(ix) Ergot alkoloids;

(x) Compounds which modulate the action of natruretic factors ~~in~~

particular atrial naturetic factor (also known as atrial naturetic peptide), B type and C type naturetic factors such as inhibitors or neutral endopeptidase;

(xi) Angiotensin receptor antagonists such as losartan;

(xii) Substrates for NO-synthase, such as L-arginine;

(xiii) Calcium channel blockers such as amlodipine;

(xiv) Antagonists of endothelin receptors and inhibitors or endothelin-converting enzyme;

(xv) Cholesterol lowering agents such as statins (e.g. atorvastatin/ Lipitor- trade mark) and fibrates;

(xvi) Antiplatelet and antithrombotic agents, e.g. tPA, uPA, warfarin, hirudin and other thrombin inhibitors, heparin, thromboplastin activating factor inhibitors;

(xvii) Insulin sensitising agents such as rezulin and hypoglycaemic agents such as glipizide;

(xviii) L-DOPA or carbidopa;

(xix) Acetylcholinesterase inhibitors such as donezipil;

(xx) Steroidal or non-steroidal anti-inflammatory agents;

(xxi) Estrogen receptor modulators and/or estrogen agonists and/or estrogen antagonists;

(xxii) A PDE inhibitor, more particularly a PDE 2, 3, 4, 5, 7 or 8 inhibitor, preferably PDE2 or PDE5 inhibitor and most preferably a PDE5 inhibitor;

(xxiii) An NEP inhibitor;

(xxiv) Vasoactive intestinal protein (VIP), VIP mimetic, VIP analogue, more particularly mediated by one or more of the VIP receptor subtypes VPAC1,VPAC or PACAP (pituitory adenylate cyclase activating peptide), one or more of a VIP receptor agonist or a VIP analogue or a VIP fragment, one or more of a α-adrenoceptor antagonist with VIP combination;

(xxv) A melanocortin receptor agonist or modulator or melanocortin enhancer;

(xxvi) A serotonin receptor agonist, antagonist or modulator, more particularly agonists, antagonists or modulators for 5HT1A (including VML 670), 5HT2A, 5HT2C, 5HT3 and/or 5HT6 receptors;

(xxvii) A testosterone replacement agent ~~(including dehydroandrostendione)~~, testosternone ~~(Tostrelle)~~, dihydrotestosterone or a testosterone implant;

(xxviii) Estrogen, estrogen and medroxyprogesterone or medroxyprogesterone acetate (MPA) ~~(i.e. as a combination)~~, or estrogen and methyl testosterone hormone replacement therapy agent;

(xxix) A modulator of transporters for noradrenaline, dopamine and/or serotonin;

(xxx) A purinergic receptor agonist and/or modulator;

(xxxi) A neurokinin (NK) receptor antagonist;

(xxxii) An opioid receptor ~~agonist, antagonist or~~ modulator~~, preferably agonists for the ORL-1 receptor~~;

(xxxiii) An agonist or modulator for oxytocin/vasopressin receptors, ~~preferably a selective oxytocin agonist or modulator~~;

(xxxiv) Modulators of cannabinoid receptors;

(xxxv) A bombesin receptor antagonist~~, more particularly a bombesin BB_1, BB_2, BB_3, or BB_4 receptor antagonist, preferably a bombesin BB_4 inhibitor~~;

(xxxvi) A SEP inhibitor; or

(xxxvii) An agent capable of modulating the activity of an intermediate conductance calcium-activated potassium (IK_{Ca}) channel in the sexual genitalia of an individual.

Please amend claim 35 as follows:

Claim 35 (Amended) A method of treating or preventing MED by administering ~~The use of~~ a combination consisting of one or more NPYi's and one or more PDEi's to an individual ~~in the manufacture/preparation of a medicament for the treatment or prevention of MED~~.

Please amend claim 36 as follows:

Claim 36 (Amended) A method according to claim 35 ~~The use according to claim 35~~ wherein said NPYi is an NPY Y1i.

Please amend claim 37 as follows:

Claim 37 (Amended) A method according to claim 36 ~~The use according to claim 35 or claim 36~~ wherein said PDEi is a PDE5i.

Please amend claim 38 as follows:

Claim 38 (Amended) A method according to claim 37 ~~The use according to any one of claims 35-37~~ wherein the medicament is administered by mouth.

Please amend claim 41 as follows:

Claim 41 (Amended) A pharmaceutical composition according to claim 40 ~~claims 39 or 40~~ wherein said NPY Y1i is highly selective for NPY Y1 receptors associated with genitalia.

Please amend claim 42 as follows:

Claim 42 (Amended) A pharmaceutical composition according to ~~claim 39 or~~ claim 41 wherein said PDEi is a PDE5i.

Please amend claim 43 as follows:

Claim 43 (Amended) A pharmaceutical composition according to ~~any one of claims 39 to~~ claim 42 wherein the composition is administered by mouth.

Please amend claim 44 as follows:

Claim 44 (Amended) A method of treating or preventing MED by administering ~~The use of~~ a pharmaceutical composition according to claim 43 ~~any one of claims 39-43 in the preparation of a medicament for the treatment or prevention of MED~~.